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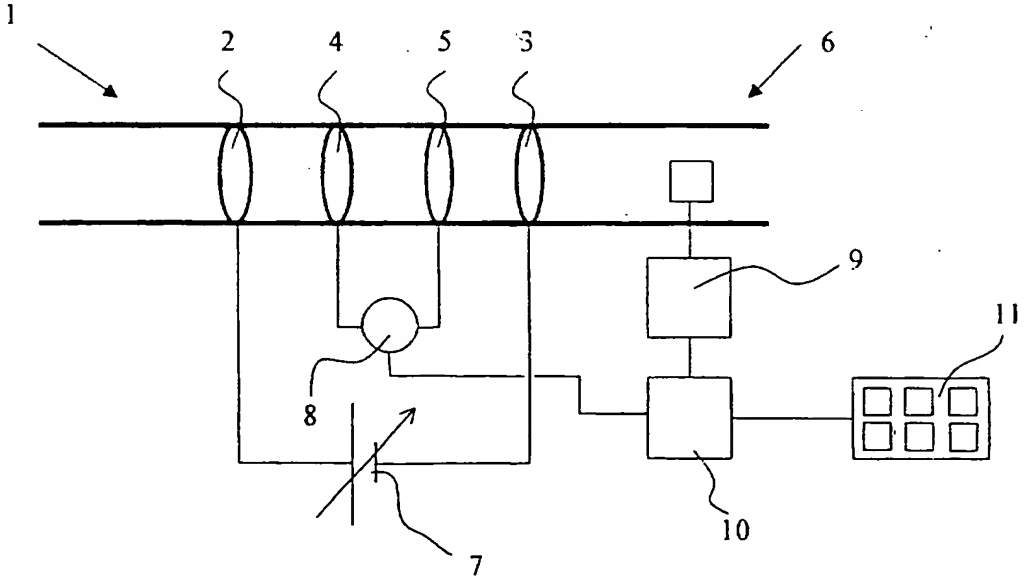
(54) Title: HEART-LUNG MACHINE PROVIDED WITH A DEVICE FOR ELECTRICAL IMPEDANCE MEASUREMENT, AND METHOD THEREFORE




(57) Abstract: The invention relates to a blood transporting machine, at least comprising transport means for transporting blood, wherein the blood transporting machine is further provided with a device for electrical impedance measurement of the blood, which comprises means for generating an electrical current in the blood, means for measuring the electrical impedance and means for recording the electrical impedance and/or impedance change in the blood. The blood transporting machine also comprises processing means for processing recorded impedance to a blood viscosity value.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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# HEART-LUNG MACHINE PROVIDED WITH A DEVICE FOR ELECTRICAL IMPEDANCE MEASUREMENT, AND METHOD THEREFORE

The present invention relates to a blood transporting machine as according to the heading of claim 1.

A blood transporting machine is used for extracorporeal circulation of blood. Examples hereof are a heart-lung machine and an artificial kidney machine.

An open-heart operation is usually performed with a heart-lung machine (HLM). Cerebral dysfunction and to a lesser extent kidney function disorders are frequently occurring problems for patients as a result of this operation. These cerebral and renal problems not only cause a greater or lesser degree of permanent invalidity for the patient, but also result in hospital accommodation costs in the short term and costs of care in the longer term.

One of the causes of renal and cerebral disorders is formed by a rise in the viscosity of the blood, which is caused by hypothermia and by the "acute phase" reaction generated in the body by the operation. Increased viscosity is linked to reduced cerebral microcirculation. Hyperviscosity resulting from hypothermia affects the renal function. In addition, the moments of canulating, manipulation of the heart and declamping of the aorta are significant surgical sources of the occurrence of microembolisms. Despite the use of different filters in conjunction with the HLM, a significant part of the microembolisms is still found to occur as a result of perfusion problems associated with the HLM.

The present invention has for its object to monitor the viscosity of blood when it is transported extracorporeally by a blood transporting machine.

This objective is achieved with the present invention by providing a blood transporting machine of the above stated type, further comprising means for processing the impedance value to a viscosity value. The blood viscosity

of a patient being treated can be measured with the blood transporting machine according to the invention.

It is favourable to embody the blood transporting machine as according to claim 2. It is hereby possible to monitor the blood viscosity value during open-heart operations. When the recorded blood viscosity value changes in adverse manner, external intervention can take place, for instance with medication.

Claim 3 is preferably applied. The electrical impedance measurement in the blood hereby takes place as soon as it is transported out of the blood transporting machine. A viscosity value for the blood is hereby obtained in a short time.

Claim 4 is preferably applied. Measuring of the impedance of the blood hereby becomes possible in efficient manner.

According to claim 5 the blood transporting machine is preferably embodied with a set of measuring electrodes. The impedance of the blood can hereby be measured between the measuring electrodes.

In the preferred embodiment the electrodes are circular. Such an embodiment allows the electrodes to enclose the perfusion tube.

The blood transporting machine is preferably embodied with platinum electrodes. The use of platinum electrodes has a favourable effect on the accuracy of the value determination of the viscosity of the blood.

The electrodes are preferably arranged at a regular distance from each other in the longitudinal direction of the perfusion tube. A homogeneous electrical field in the blood is hereby achieved.

It is favourable to embody the heart-lung machine as according to claim 9. Such a ratio is effective for the homogeneity of the electrical field to be applied and measured.

The measure as according to claim 10 has a favourable effect on the accuracy of the measurement of the

impedance value, and therefore on the accuracy of the blood viscosity to be determined.

In a preferred embodiment according to the invention the measure of claim 11 is applied in the blood transporting machine. Particular medications administered to a patient when blood is circulated outside the body influence the sodium concentration in the blood of the patient. The sodium concentration influences the impedance of the blood. Inclusion of the sodium concentration in the algorithm for processing the impedance signal produces a more accurate determination of the viscosity value of the blood.

The invention also relates to and provides a method for the operation of the heart-lung machine according to the invention. The method according to the invention relates in particular to detecting embolisms in the blood.

The method according to the invention preferably comprises of detecting air embolisms and/or micro-emboLisms.

In a preferred embodiment according to the invention the blood transporting machine is embodied with temperature measuring means and means for measuring the haematocrit value of the blood. These values can hereby also be monitored. The relation between the electrical impedance of the blood and the viscosity depends on the temperature and is also determined by the haematocrit value. For processing of the impedance signal to a viscosity value a calculation of the impedance signal is necessary with an algorithm dependent on the temperature and the haematocrit value.

It is favourable to determine correlation values for the relation between impedance of the blood and viscosity in relation to the temperature and the haematocrit value. The correlation coefficients are determined by doing an experiment with a large group of people. These are incorporated in the algorithm for processing the impedance signal to a viscosity value.

An apparatus and a method for detecting the presence of embolisms in a tube through which blood or other fluid flows using a blood impedance measuring system is otherwise known from US 4,014,206.

The invention is further elucidated with reference to the annexed figures, in which:

Figure 1 shows a schematic view of a preferred embodiment of the device for electrical impedance measurement of the blood in a heart-lung machine;

Figure 2 shows a graph of a measurement signal for the impedance with the embodiment of figure 1;

Figure 3 shows a graph of an example of change in the impedance in accordance with a measurement with the embodiment of figure 1;

Figure 4 shows a schematic view of a device for electrical impedance measurement of the blood, wherein particles flow in the blood;

Figure 5 shows a graph of the relation between impedance and viscosity corrected according to the invention.

Figure 1 shows a schematic view of a preferred embodiment of the measuring device 1 for electrical impedance measurement of the blood in a blood transporting machine. The measuring device of the blood transporting machine comprises two outer current electrodes 2,3 and two inner measuring electrodes 4,5 in the perfusion tube 6, immediately after the source from the blood transporting machine. Electrodes 2-5 are preferably circular and of platinum or stainless steel with a layer of precious metal. In order to obtain a homogeneous electrical field the distances between electrodes 2-5 are chosen so as to be more than twice the diameter of the perfusion tube 6 coming out of the blood transporting machine. By generating a low alternating current (10mA - 1mA) with a frequency between 4 kHz and 5000 kHz with an alternating current source 7 via the two outer electrodes 2,3, it will be possible via measuring electrodes 4,5 to continuously measure an impedance (ZO) of the blood

passing the measuring electrodes. The impedance is acquired by measuring means 8.

Also shown is a sodium concentration measuring means 9 which is arranged in perfusion tube 6. Processing means 10 processes the measured value to a blood viscosity value which can be shown on a screen 11. The processing means can also be embodied to detect the occurrence of embolisms in the blood, air and/or micro-embolisms in particular.

An example of an impedance signal as measured with the embodiment of figure 1 is shown in figure 2. A continuous recording of the change in the impedance signal (delta Z) can likewise take place. An example of a measurement signal of the change in the impedance signal is shown in figure 3.

It is known that blood has electrical properties. These electrical properties differ for plasma and blood cells. The plasma and the interior of the cells consist of conducting fluids with a determined electrical resistance and cell membranes consist of phospholipids and proteins with di-electrical properties. The electrical impedance of blood is determined primarily by three parameters: plasma resistance, internal resistance in the cell and the capacitance of the cell membrane. The electrical impedance of the blood increases with an increased viscosity of the blood. Just as the viscosity, the electrical impedance of blood increases during hypothermia and this is determined to a large degree by the haematocrit.

Small particles (< 100 micron) with an impedance other than blood will become manifest in a sudden change in the impedance signal (Figures 2 + 3). These changes can be seen particularly in the deltaZ signal and the magnitude of this change depends on the difference in specific resistance of the particles and of blood. During passage of air particles a large deflection will occur in the deltaZ signal in view of the clearly higher specific resistance of air relative to blood. This deflection of

the deltaZ signal will be less great during passage of particles of other consistency, such as in the case of small clots, the specific resistance of which differs to a lesser degree from the specific resistance of blood. The deflection of the impedance signal will therefore not only indicate whether or not small particles are passing such as micro-embolisms but, by means of the characteristics of the impedance at different frequencies, will also provide insight into the consistency of these particles, i.e. whether there are air embolisms due to for instance leakage in the perfusion system or micro-embolisms of thrombotic material. In both cases the treatment of the problem will be very different. When there are indications of small thrombi the anticoagulant will have to be adjusted, and in the case air is present it will be necessary to search for leakage in the perfusion system.

Not only can the impedance signal provide insight into the presence or otherwise and consistency of particles with impedance other than that of blood, but when the continuous flow speed through the perfusion tubes is known the total time of change in the impedance signal will also provide some information about the diameter of the particle parallel to the line between the measuring electrodes (see Figure 4).

Another method of monitoring the coagulation during OHO with HLM by means of on-line bio-impedance measurements occurs when fibrinogen-reducing agents are used instead of heparin as anticoagulation therapy. Comparative tests have shown that the chance of thrombotic complications on the one hand and haemorrhagic complications on the other during an open-heart operation does not differ significantly for heparin and a fibrinogen-reducing medication such as Ancrod. Earlier in-vitro bio-impedance research has shown that there is a high correlation between the measured impedance of blood and the concentration of fibrinogen that is present, and therefore between the impedance and the viscosity of the blood. The impedance of blood decreases as the viscosity and concen-

tration of fibrinogen become lower; other factors influencing the impedance, such as haematocrit and temperature in particular, have to be held constant. In order to maintain a target concentration of fibrinogen during OHO by means of for instance Ancrod, the dosing of the Ancrod can be titrated on the basis of continuous impedance measurements. The impedance can again be measured by means of the same arrangement of four electrodes (two current electrodes and two measuring electrodes) in the perfusion tube (see figure 1). The impedance values which correlate best with the fibrinogen concentration are the Rp and Cm. These can be calculated by successively measuring the impedance within a few seconds at at least three different current frequencies (e.g. 4 kHz, 512 kHz and 2000 kHz).

The measurement of the viscosity value can also be used for another purpose. In view of the contact of the blood with the foreign surface in the blood transporting machine, there is a risk of an "acute phase" reaction, wherein there is an increase in the viscosity of the blood. An increased viscosity of the blood taken up again into the circulation of the patient can cause problems, particularly in respect of arterioles and microcirculator level. This could cause post-operative neurological problems. During an OHO there occur many anti-inflammatory reactions with the release of "acute phase" proteins, which are known to adversely affect the blood in rheological sense. Such a systematic anti-inflammatory reaction even occurs in a heart operation without extracorporeal circulation.

Continuous measurement of the impedance of the blood can provide insight into the viscosity changes of blood and viscosity-reducing therapy can optionally be given on the basis of the findings. Just as the viscosity, the electrical impedance of blood increases during hypothermia and this is determined in large measure by the haematocrit value.

According to the invention a relation can be formulated between the viscosity value, the electrical impedance, the haematocrit value, the temperature and the sodium level in the blood. The latter three factors influence the impedance of the blood. A test arrangement with blood from ten volunteers was used to establish correlation coefficients for said relation. The test arrangement simulated a heart-lung machine. Gelofusine was also added to change the haematocrit value. It was found that:

(1) $\ln(\text{visco}) = 0.774 + 2876 \times 10^{-2} \times HCT - 2.104 \times 10^{-2} \times T + 2.765 \times 10^{-3} \times Na$.

(2) $\ln(\text{imp.}) = 5.466 + 2.386 \times 10^{-2} \times HCT - 1.961 \times 10^{-2} \times T - 5.995 \times 10^{-3} \times Na$.

(3) $\text{Visco} = 0.364 + 3.782 \times 10^{-2} \times \text{imp.}$,

wherein Ln is the natural logarithm, visco is the viscosity value, HCT the haematocrit value, T the temperature, Na the sodium level, and imp. the impedance according to the measurement. Measurement took place in the test arrangement with an alternating current with a frequency of 20 kHz and an alternating current value of 300 $\mu$A.

During the test arrangement the levels of Ht, sodium, potassium, calcium and the pH were measured. Of these variables only the sodium was found to have significant influence on the impedance/viscosity. For the processing of the impedance measurement to a viscosity value a correction is therefore necessary which depends on the measured sodium concentration.

The third formula shows a direct correlation between the viscosity value and the impedance measurement.

In figure 5 is shown the correlation between the viscosity and the impedance of a test measurement with the blood of ten people. The viscosity and impedance are shown to be correlated. The measurement of the impedance can be used to determine the viscosity value. The processing means are provided with an algorithm which calculates the relation according to formula (3), wherein a

correction for the measured sodium concentration is also carried out.

## CLAIMS

1. Blood transporting machine, at least comprising transport means for transporting blood, wherein the blood transporting machine is further provided with a device for electrical impedance measurement of the blood, which comprises means for generating an electrical current in the blood, means for measuring the electrical impedance and means for recording the electrical impedance and/or impedance change in the blood, **characterized in that** the blood transporting machine also comprises processing means for processing recorded impedance to a blood viscosity value.

2. Blood transporting machine as claimed in claim 1, **characterized in that** the machine is provided with means for functioning as heart-lung machine.

3. Blood transporting machine as claimed in claim 1, **characterized in that** transport means comprise at least one perfusion tube and the current generating means and the measuring means are arranged in the perfusion tube close to the source thereof out of the blood transporting machine.

4. Blood transporting machine as claimed in claim 1, 2 or 3, **characterized in that** the current generating means comprise a set of current generating electrodes which are connected to a source of alternating voltage and which can generate an alternating current in the blood.

5. Blood transporting machine as claimed in any of the claims 1-4, **characterized in that** the measuring means comprise a set of measuring electrodes.

6. Blood transporting machine as claimed in claim 4 or 5, **characterized in that** the electrodes are circular.

7. Blood transporting machine as claimed in claim 4, 5 or 6, **characterized in that** the electrodes are platinum electrodes.

8. Blood transporting machine as claimed in any of the foregoing claims 1-7, **characterized in that** the electrodes are arranged at a regular distance from each other in the perfusion tube in the direction of the blood flow.

9. Blood transporting machine as claimed in claim 8, **characterized in that** the distance is at least twice the diameter of the perfusion tube.

10. Blood transporting machine as claimed in any of the foregoing claims, **characterized in that** in the direction of the blood flow the current generating electrodes comprise the outer electrodes and the measuring electrodes the inner electrodes.

11. Blood transporting machine as claimed in any of the foregoing claims, **characterized in that** means are also arranged for measuring the sodium concentration in the blood.

12. Blood transporting machine as claimed in claim 11, **characterized in that** the processing means can correct the blood viscosity value for the measured sodium concentration.

13. Blood transporting machine as claimed in any of the foregoing claims, **characterized in that** means are also arranged for measuring the haematocrit value of the blood.

14. Blood transporting machine as claimed in any of the foregoing claims, **characterized in that** the processing means determine the viscosity value with an algorithm for the impedance measurement, wherein the algorithm depends on the temperature and the haematocrit value.

15. Blood transporting machine as claimed in any of the foregoing claims, **characterized in that** the algorithm comprises correction coefficients for the dependence of the viscosity value on temperature and haematocrit value during an impedance measurement.

16. Use of a blood transporting machine as claimed in any of the foregoing claims for detecting the occurrence of embolisms in the blood.

17. Use as claimed in claim 13, **characterized in that** the embolisms comprise air embolisms and/or microembolisms.

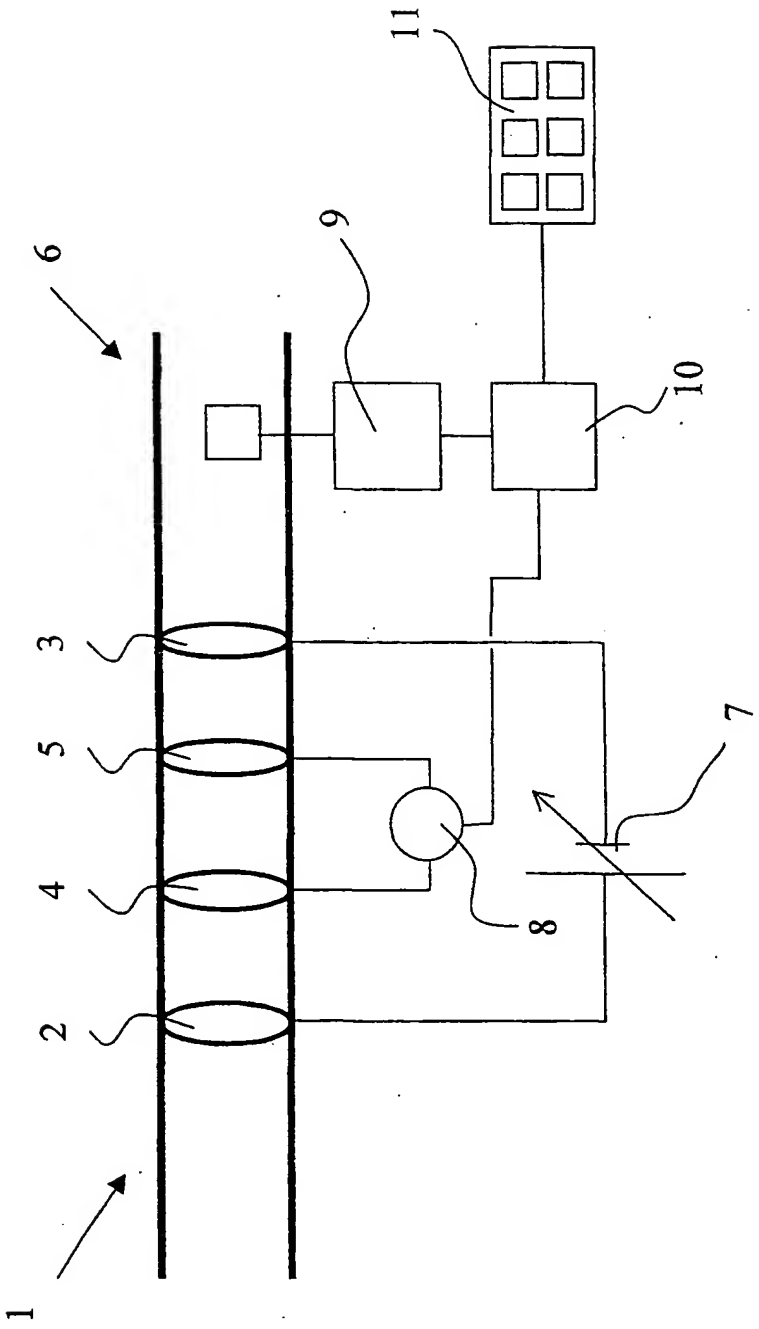


FIG.1

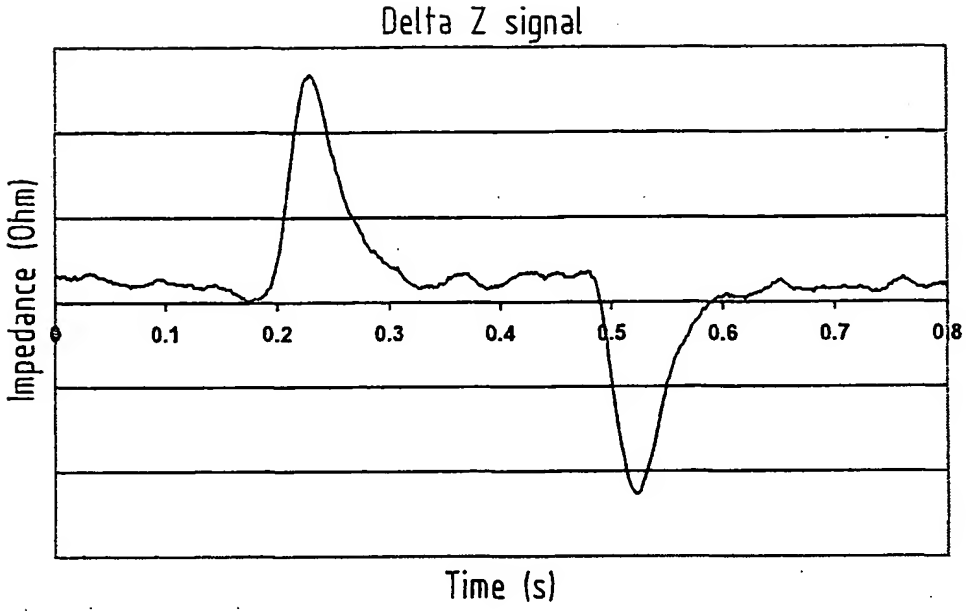


FIG. 3

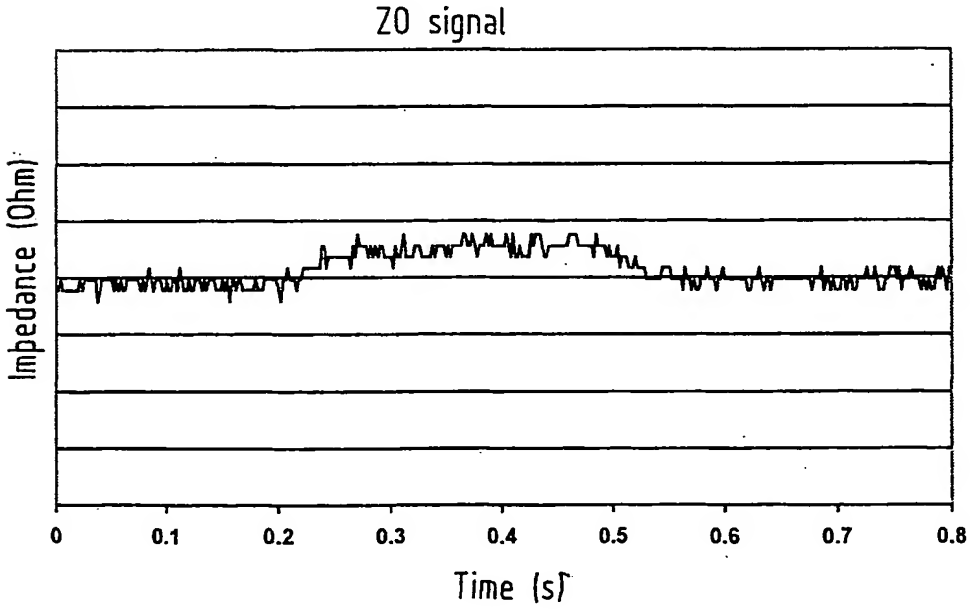


FIG. 2

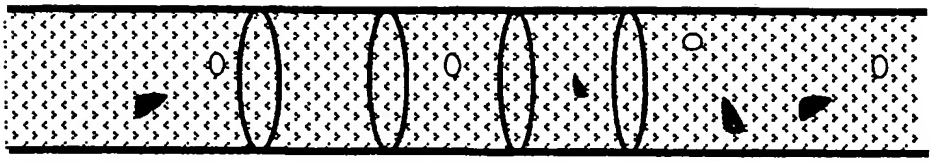

FIG. 4

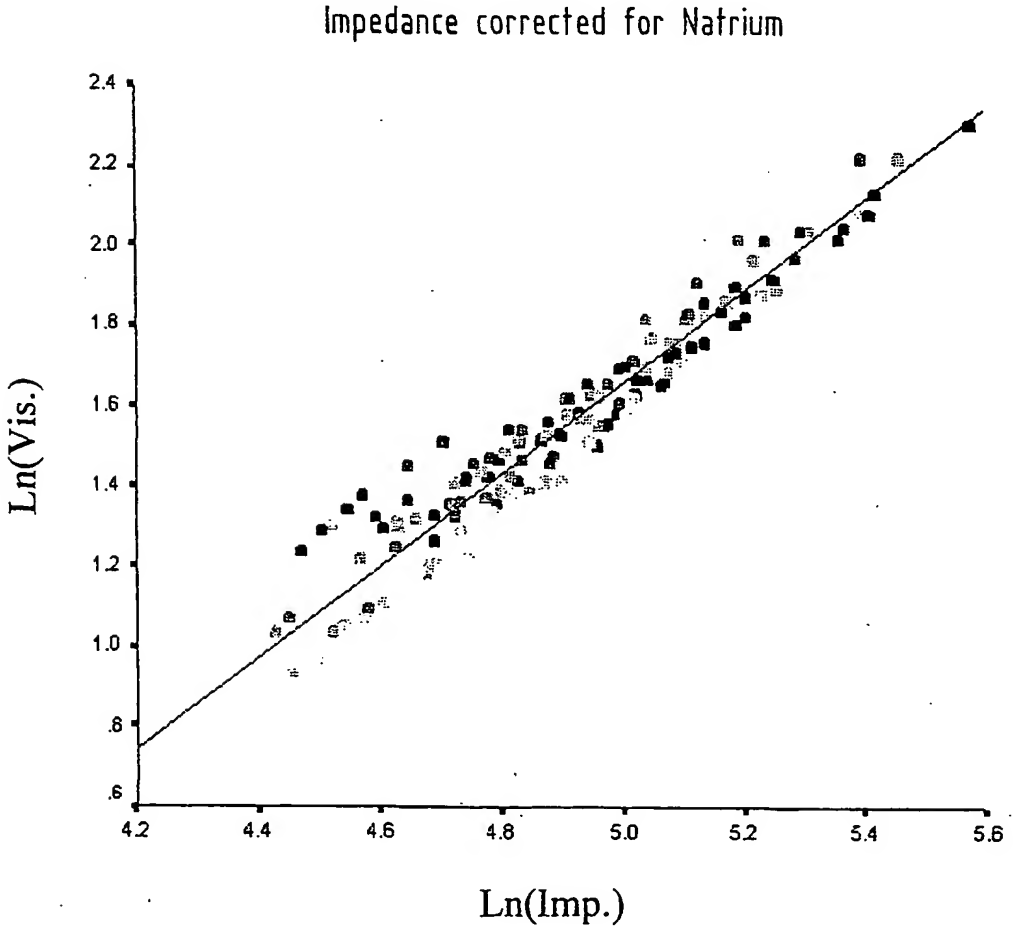


FIG. 5

# INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/487 A61M1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 28 January 2002 | 04/02/2002 |

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